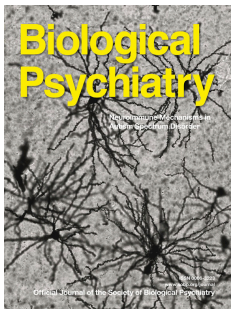
DOI:
10.1016/j.biopsych.2017.07.008

Document Version
Peer reviewed version

Accepted Manuscript



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PII: S0006-3223(17)31807-3

DOI: 10.1016/j.biopsych.2017.07.008

Reference: BPS 13270

To appear in: *Biological Psychiatry*

Received Date: 20 May 2016

Revised Date: 6 July 2017

Accepted Date: 6 July 2017

Please cite this article as: Noordermeer S.D.S., Luman M., Greven C.U., Veroude K., Faraone S.V., Hartman C.A., Hoekstra P.J., Franke B., Buitelaar J.K., Heslenfeld D.J. & Oosterlaan J., Structural Brain Abnormalities of Attention-Deficit/Hyperactivity Disorder with Oppositional Defiant Disorder, *Biological Psychiatry* (2017), doi: 10.1016/j.biopsych.2017.07.008.

Structural Brain Abnormalities of Attention-Deficit/Hyperactivity Disorder with Oppositional Defiant Disorder

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Key words: Structural MRI; Cortical Thickness; SBM; ADHD; Comorbidity; ODD

Word count abstract: 250 words

Word count article body: 4000 words

Number of Tables: 2

Number of Figures: 3

Number of Supplements: 4

Short Title: Structural Brain Abnormalities of ADHD and Comorbid ODD

Abstract

Background: Attention-Deficit/Hyperactivity-Disorder (ADHD) is associated with structural abnormalities in total gray matter, basal ganglia and cerebellum. Findings of structural abnormalities in frontal and temporal lobes, amygdala, and insula are less consistent. Remarkably, the impact of comorbid Oppositional Defiant Disorder (ODD) (comorbidity rates up to 60%) on these neuroanatomical differences is scarcely studied, while ODD (in combination with Conduct Disorder (CD)) has been associated with structural abnormalities of the frontal lobe, amygdala, and insula. The aim of this study was to investigate the effect of comorbid ODD on cerebral volume and cortical thickness in ADHD.

Methods: Three groups (mean age 16 year, SD=3.5, range 7-29) were studied on volumetric and cortical thickness characteristics using structural magnetic resonance imaging (Surface-Based Morphometry): ADHD+ODD (*n*=67), ADHD-only (*n*=243), and controls (*n*=233). Analyses included moderators age, gender, IQ, scan-site.

Results: ADHD+ODD and ADHD-only showed volumetric reductions in total gray matter and (mainly) frontal brain areas. Stepwise volumetric reductions (ADHD+ODD<ADHD-only<controls) were found for mainly frontal regions, and ADHD+ODD was uniquely associated with reductions in several structures (e.g. the precuneus). In general, findings remained significant after accounting for ADHD symptom-severity. There were no group differences in cortical thickness. Exploratory voxel-wise analyses showed no group differences.

Conclusions: ADHD+ODD and ADHD-only were associated with volumetric reductions in brain areas crucial for attention, (working) memory and decision-making. Volumetric reductions of frontal lobes were largest in the ADHD+ODD group, possibly underlying observed larger impairments in neurocognitive functions. Previously reported striatal abnormalities in ADHD may be due to comorbid CD, rather than ODD.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood psychiatric disorders and is defined by developmentally inappropriate levels of inattention, and/or hyperactivity-impulsivity (1). Neuroanatomical findings most consistently reported for ADHD are reduced total gray matter volume and reduced volume of the basal ganglia and the cerebellum. For the latter, cortical thickness abnormalities are also associated with ADHD. Additionally, volumetric reductions and reduced cortical thickness of the frontal and temporal lobes have been reported, although less consistently (see for reviews; 2,3). Finally, some studies reported volumetric abnormalities in the amygdala and insula to be related to ADHD, but especially for the amygdala findings are very inconsistent (4-9).

A potential explanation for the inconsistent neuroanatomical findings may be the presence of comorbid disorders in the studied ADHD samples, such as Oppositional Defiant Disorder (ODD). ODD is present in up to 60% of clinically referred children with ADHD (10-12), and is defined by a persistent pattern of irritable and angry mood, vindictiveness and developmentally inappropriate, negativistic, defiant, and disobedient behavior toward authority figures (1). Compared with individuals with only ADHD or ODD, individuals with ADHD+ODD show an earlier age of onset for both ADHD and ODD symptoms, exhibit more physical aggression and delinquency, show more functional impairments such as poorer working memory, inhibition, temporal processing, and emotion recognition, and have a considerably worse prognosis (11,13,14).

Surprisingly, the majority of studies on neuroanatomical correlates of ADHD did not investigate or report on the presence of comorbidities such as ODD, resulting in relatively few studies investigating ADHD-only samples. The few studies in ADHD-only samples were less likely to find volumetric abnormalities in the frontal cortex than studies that included comorbid individuals (for an overview see 15). They also showed that accounting for the presence of comorbid ODD significantly influenced findings, with either larger abnormalities in individuals with ADHD+ODD (16), or more abnormalities

associated with ADHD after controlling for comorbid ODD (17). Furthermore, studies assessing ADHD-only groups showed no volumetric abnormalities in the amygdala (4,6,7), and abnormalities in the insula were accounted for by comorbid ODD (8). For cortical thickness, an influential study showed a delay in cortical development for individuals with ADHD, but of that sample 35% of the individuals had a comorbid diagnosis of ODD (3,18). Thus, previous findings may not purely reflect neuroanatomical characteristics of ADHD, but may be confounded by comorbid ODD.

An alternative explanation for the inconsistent neuroanatomical findings for ADHD could be the age of included participants. According to the maturational delay hypothesis (18), individuals with ADHD show a maturational lag in brain development compared with typically developing individuals. According to this theory, the maturational lag is most prominent in prefrontal regions and has been reported to correspond with a three year delay, with typically developing individuals attaining their peak cortical thickness at the age of 7.5 years and individuals with ADHD at the age of 10.5 years (18). Additionally, it has been reported that structural abnormalities in the basal ganglia normalize with age (2,19). However, in contrast with the maturational delay hypothesis, structural abnormalities in the anterior cingulate cortex seem to persist into adulthood (2,20). Hence, studying the impact of comorbid ODD and age is pivotal to understanding the heterogeneity in findings.

So far, no studies on neuroanatomical correlates exclusively focused on individuals with ODD-only or on ADHD with comorbid ODD (ADHD+ODD). Rather, studies included mixed samples of children with ADHD with and without comorbid ODD, or included children with both (comorbid) ODD and conduct disorder (CD; a related disorder for which ODD is often a precursor) (21). The studies that focused on volumetric characteristics of individuals with ODD/CD with and without comorbid ADHD consistently reported reduced volumes of the amygdala, insula and frontal lobe (see for review; 21). Furthermore, it has been reported that CD is associated with volumetric abnormalities in frontal areas, while this association seemed relatively weak for ADHD-only (15). In terms of cortical thickness, one

study investigated an ODD/CD sample and reported a decreased overall mean cortical thickness and thinning of the cingulate, prefrontal and insular cortices (22).

To summarize, while neuroanatomical abnormalities in ADHD-only appear to be most strongly related to the frontal regions, ADHD+ODD appears associated with abnormalities in the frontal regions, amygdala, and insula. The overlap in affected brain areas may explain inconsistencies in reported abnormalities for frontal areas in ADHD, as these may be driven (partly) by the presence of comorbid ODD or by a combined effect of both disorders. So far, the literature does not answer the question on whether previously reported abnormalities in ADHD reflect neuroanatomical characteristics of ADHD or rather of comorbid ODD. Therefore, a comparison between individuals with ADHD+ODD and individuals with ADHD-only would be highly informative in terms of specificity of findings for ADHD. This may also clarify whether previously reported structural abnormalities in the amygdala and insula were driven by comorbid ODD.

The current study aimed to disentangle brain abnormalities associated with ADHD versus ADHD+ODD by comparing these diagnostic groups to typically developing peers across a broad age range from childhood to late adolescence. We studied the impact of age on in order to test whether individuals with ADHD showed a maturational delay in neuroanatomical development. To meet these aims, neuroanatomical volumes and cortical thickness were compared between a large sample of individuals with ADHD without ODD (ADHD-only), individuals with ADHD and ODD (ADHD+ODD), and typically developing controls. We hypothesized that (a) abnormalities in the basal ganglia and cerebellum would be strongly associated with ADHD and therefore present in both diagnostic groups; (b) abnormalities in the amygdala and the insula would be driven by ODD rather than by ADHD and hence would be predominantly present in the ADHD+ODD group rather than the ADHD-only group. Furthermore, we speculated that (c) abnormalities in the frontal lobes would be more pronounced in

the ADHD+ODD group than in the ADHD-only group, but present in both, since previous studies have implicated the frontal lobe in both ADHD and ODD.

Methods

Participants

Participants were selected from the NeuroIMAGE cohort (for full description see S1 and 23). Inclusion criteria for the current study were: European Caucasian descent, IQ≥80 (as estimated with the Vocabulary and Block Design subtests of an age-appropriate Wechsler-test (3rd edition), no diagnosis of autism/Asperger's/anxiety disorder/depression/epilepsy/general learning difficulties/brain disorders/known genetic disorders (e.g. Fragile X syndrome, Down syndrome). Controls were not allowed to have a past or current diagnosis of ADHD, ODD, or any other psychiatric disorder. A total of 1069 participants contributed data to NeuroIMAGE: 751 participants from ADHD-families (participants in the ADHD-only or ADHD+ODD group and their biological siblings) and 318 participants from control-families (participants in the control group and their biological siblings(23). For the current study only individuals with a current ADHD diagnosis, with (n=67) and without comorbid ODD (n=243) and typically developing individuals (n=233), were included. Not all participants in the NeuroIMAGE study underwent a magnetic resonance imaging (MRI) scanning session due to contraindications for MRI.

Diagnostic Assessment

A full description is provided in previous work (see S1 and 24). In short, participants were diagnosed with ADHD or ODD according to DSM-IV criteria. Individuals in the ADHD+ODD group qualified for a diagnosis of both ADHD diagnosis and ODD, while individuals in the ADHD-only group only qualified for a diagnosis of ADHD. A diagnostic algorithm was applied to create a combined symptom count from the questionnaires and interview.

MRI acquisition and analysis

MRI data were acquired at 1.5 Tesla on a Siemens Sonata scanner (Amsterdam) and on a Siemens Avanto scanner (Nijmegen). Both sites used a standard identical 8-channel phased array coil and closely matched scanparameters (S1).

Cortical reconstruction and volumetric segmentation were performed with FreeSurfer software version 5.3 with default settings (http://surfer.nmr.mgh.harvard.edu/), see S1 for the investigated areas and quality assurance procedures. FreeSurfer is an image processing pipeline including a volume-based route to subcortical segmentation (25), and a surface-based route to create a 3D reconstruction and parcellation of the cortical sheet (26,27). From FreeSurfer parcellations and segmentations (27), we calculated total gray matter volume, total cortical matter volume and cortical and subcortical volumes, as well as bilateral volumes for each brain region. In addition, FreeSurfer was used to calculate cortical thickness measures. Regions were based on the Desikan-Killiany atlas (27), and an overview of investigated areas can be found in Supplement 1.

Procedure

The current study was part of a comprehensive assessment protocol encompassing phenotypic, neurocognitive, and MRI assessments (23), see S1 for details. Informed consent was signed by all participants (for participants <12 years only parents signed informed consent, for participants 12-18 years old both the participants and their parents signed, for participants >18 years only the participants signed). The study was approved by the local ethics committees.

Statistical analyses

Groups were compared on demographic characteristics using analysis of variance (ANOVA) or chi-square tests. All analyses that tested group differences in neuroanatomical characteristics were performed using SPSS Mixed Models (version 21.0). Mixed model analyses were performed with a random intercept, with an exchangeable structure for family, to account for the hierarchical structure due to family relations (siblings with ADHD in the diagnostics group or siblings without ADHD in the control

group) in the data. Group differences were examined as a fixed effect. To correct for multiple testing, False-Discovery Rate (FDR)-corrected results were reported (maximum acceptable FDR of 5%), based on the sequential Benjamini-Hochberg FDR-correction algorithm (28). When an overall significant main effect of group was found, post-hoc pairwise group comparisons (LSD) were assessed.

Linear interaction effects between group and possible moderator variables (age [linear/nonlinear], gender, IQ, medication use, scan-site) were assessed. When a significant interaction effect was present, the main effect of the moderator and interaction effect between group and moderator were added to the model. In that case, interactions were plotted to clarify the direction of the interaction. When the interaction term was not significant, but only a main effect was found, the variable was included in the model as a covariate.

Results

A total of 542 participants took part in this study: 67 participants with ADHD+ODD, 243 participants with ADHD-only, and 233 typically developing controls. Mean age was 16 years (SD=3.5, range 7-29), and individuals from the three groups where similarly spread out across the age range. Table 1 shows further group characteristics. The diagnostic groups did not differ from the typically developing group in age (p>.225, both diagnostic groups), but did differ in IQ (p<.001, both diagnostic groups; higher IQ in control group), and gender (p<.001 for ADHD-only, p=.026 for ADHD+ODD; more females in control group). Furthermore, the diagnostic groups showed higher levels of total ADHD, hyperactive and inattentive symptoms, and ODD symptoms, compared with the control group (p<.001 for both diagnostic groups; less symptoms in control group). The ADHD+ODD and ADHD-only groups did not differ from each other in IQ (p=.532) or gender (p=.803). However, compared with the ADHD-only group, the ADHD+ODD group showed a higher level of ODD symptoms (p<.001), as well as a higher level of total (p<.001), hyperactive (p=.021), and inattentive (p<.001) ADHD symptoms. Given these differences in ADHD symptom count

between diagnostic groups, sensitivity-analyses were performed for those regions for which group differences were observed between the diagnostic groups. For these analyses, total ADHD symptom count was entered as covariate.

We found no significant interactions between group and gender, IQ, medication use, or scan-site. However, age (linear only), gender, IQ, and scansite, added significantly to the model for the majority of the structures. Therefore, these variables were included as covariates in all models. For the volumetric analyses total intracranial volume was added as additional covariate. Results for the main group comparisons are shown in Table S1 (volume) and Table S2 (cortical thickness), including the post-hoc comparisons after FDR-correction. Table 2 shows the results of the sensitivity analyses (accounting for ADHD symptom severity) for the diagnostic groups that survived FDR-correction.

Group effects

Total cortical, gray matter, and subcortical gray matter volume. For total cortical volume ($p_{FDR\text{-}corrected}$=.001) and total gray matter volume ($p_{FDR\text{-}corrected}$=.001), both diagnostic groups showed reduced volumes compared with the control group, but did not differ from each other (p=.103 and p=.126, respectively). For total subcortical gray matter volume there were no group differences.

Cortical volumes. There were several main group effects (Table S1, Figure 1-3). Post-hoc analysis showed areas for which one or both of the diagnostic groups differed from controls, and areas for which the diagnostic groups also differed from each other. Structures that showed volumetric reductions in both diagnostic groups compared with the control group included the lateral orbitofrontal (left $p_{FDR\text{-}corrected}$<.001;right $p_{FDR\text{-}corrected}$<.001), isthmus (left $p_{FDR\text{-}corrected}$=.006;right $p_{FDR\text{-}corrected}$<.001), inferior parietal gyrus (left $p_{FDR\text{-}corrected}$<.001;right $p_{FDR\text{-}corrected}$=.015), caudal middle frontal (left $p_{FDR\text{-}corrected}$=.002;right $p_{FDR\text{-}corrected}$=.002), right parahippocampal gyrus ($p_{FDR\text{-}corrected}$<.001), right medial orbitofrontal gyrus ($p_{FDR\text{-}}$

$_{corrected}$<.001), right superior frontal gyrus ($p_{FDR\text{-}corrected}$=.002), left precentral gyrus ($p_{FDR\text{-}corrected}$=.004), right rostral middle frontal gyrus ($p_{FDR\text{-}corrected}$=.005), and left lateral occipital gyrus ($p_{FDR\text{-}corrected}$=.005).

Several of the structures showed a stepwise significant reduction in volume, with the largest volumetric reduction in the ADHD+ODD group, followed by the ADHD-only group, compared with the control group. These structures were the lateral orbitofrontal, right medial orbitofrontal, right superior frontal, right caudal middle frontal, and left inferior parietal gyrus (Figure 1). Finally, there were five areas showing a disorder-specific volumetric reduction compared with controls (Figure 2). For the left rostral middle frontal ($p_{FDR\text{-}corrected}$=.002), left medial orbitofrontal ($p_{FDR\text{-}corrected}$=.004), right precuneus ($p_{FDR\text{-}corrected}$=.005), and left pars triangularis ($p_{FDR\text{-}corrected}$=.007), the ADHD+ODD group showed a reduced volume compared with both the control group and the ADHD-only group (that did not differ from each other; p=.311, p=.566, p=.087, p=.332, respectively). For the left middle temporal gyrus ($p_{FDR\text{-}corrected}$=.010), the ADHD+ODD group showed a reduced volume compared with the control group, but not compared with the ADHD-only group (p=.050). The control group and ADHD-only group did not differ (p=.104).

Results of post-hoc exploratory whole-brain-voxel-wise group comparisons showed no clusters surviving voxel-wise multiple comparisons FDR-correction. Uncorrected (p<.0001) voxel-wise results largely overlapped with the findings using an ROI approach (Figure 1, Supplementary Figures S1-S3).

Subcortical volumes. There were no main group effects for any of the subcortical structures.

Cortical thickness. There were no main group effects for cortical thickness of any of the structures (Table S2).

Effects of group by age.

We found no significant linear or quadratic interactions between group and age for any of the volumes or for cortical thickness surviving FDR-correction. Thus, the interactions were not included in the

models.

Sensitivity Analysis Diagnostic Groups

For all 11 structures that showed differences between the diagnostic groups (Table 2), the analyses were rerun for the diagnostic groups while accounting for total number of ADHD symptoms. For five of the six structures, the finding of stepwise greater volumetric reductions in the ADHD+ODD group compared with the ADHD-only group remained significant: right medial orbitofrontal $p_{FDR\text{-}corrected}$=.011, left inferior parietal gyrus $p_{FDR\text{-}corrected}$=.013, right lateral orbitofrontal $p_{FDR\text{-}corrected}$=.019, left lateral orbitofrontal $p_{FDR\text{-}corrected}$=.023, and right superior frontal $p_{FDR\text{-}corrected}$=.037. Finally, for all four structures, the ADHD+ODD-specific reduction remained significant: left rostral middle frontal $p_{FDR\text{-}corrected}$=.006, left medial orbitofrontal $p_{FDR\text{-}corrected}$=.008, left pars triangularis $p_{FDR\text{-}corrected}$=.012, and right precuneus $p_{FDR\text{-}corrected}$=.033. The disorder-specific reduction in the left middle temporal gyrus for the ADHD+ODD compared with the control group, became also significant between the ADHD+ODD and ADHD-only group (p=.044).

Discussion

We found several structures that showed volumetric abnormalities in the ADHD+ODD and/or ADHD-only group compared with typically developing controls. Frontal regions showed the hypothesized linear decrease in volume (ADHD+ODD<ADHD-only<controls). Unlike others (29), we found no lateralization for the volumetric abnormalities. After accounting for ADHD symptom severity, most of the linear volumetric reductions and all of the disorder-specific volumetric reductions for the ADHD+ODD group persisted. We found no cortical thickness abnormalities. Finally there were no interactions between group and age for our outcome measures.

Our results show that abnormalities in frontal regions are most strongly pronounced in the ADHD+ODD group compared with the ADHD-only group, in line with our hypothesis. For the left pars triangularis, left medial orbitofrontal, and left rostral middle frontal gyri, ADHD+ODD group-specific volumetric abnormalities were present. Additionally, for the lateral orbitofrontal, right medial orbitofrontal, right caudal middle frontal, and right superior frontal gyrus, a linear volumetric decrease was present, with the largest reductions in the ADHD+ODD group, followed by the ADHD-only group. Most group differences remained present after controlling for ADHD symptom severity, suggesting that these larger abnormalities are driven by both ADHD and ODD and result in a 'double burden'. This finding is in line with neurocognitive findings of impairments in inhibitory control, attention, decision making, and working memory, all functions that are heavily dependent on integrity of the (superior) frontal cortex, for both individuals with ADHD and individuals with ODD, and the observation that these neurocognitive impairments are worse in the comorbid group (3,10,30). Consistent with these findings, we found a similar linear decrease in volume of the left inferior parietal gyrus over the groups, that also remained present when controlling for ADHD severity. Thus, in line with the literature showing a neurocognitive 'double burden' for individuals with ADHD+ODD, this group also shows greater reductions in neuroanatomical volumes than individuals with ADHD-only.

The results also showed structural abnormalities in brain regions for which we had no specific hypotheses. Similar volumetric reductions in both diagnostic groups were present for global measures of total gray matter and total cortical volume. Additionally, areas with similar volumetric reductions included the isthmus of the cingulate gyrus, right parahippocampal gyrus, right inferior parietal gyrus, left lateral occipital gyrus and the left precentral gyrus. These findings are in line with previous studies showing widespread structural abnormalities in ADHD with and without comorbid ODD (2,3,20). These areas are, among others, associated with neurocognitive impairments frequently observed in individuals

with ADHD and ODD such as social learning, spatial working memory, reward processing, and motor-functioning (3,10,30-32).

Disorder-specific abnormalities for the ADHD+ODD group were observed in the right precuneus, a structure that is, among others, associated with self-reflection processing, awareness and feelings of guilt [33,34], and left middle temporal gyrus, a structure that is, among others, associated with empathic processing (33). Abnormalities of the precuneus have been related to ODD/CD in a recent meta-analysis (21), and are in line with both observed neurocognitive impairments associated with ODD and with theoretical models on ODD that suggest that impairments in social skills, such as failure to exhibit socially relevant behaviors and lack of guilt, are key features of the disorder (34-36). The left middle temporal gyrus is, among others, involved in empathic processing and has been linked to antisocial personality disorder and psychopathy, disorders that are related to ODD, and show similar behavioral problems in terms of a lack of adequate empathic responses (10,37).

There was no evidence that volumetric abnormalities in the basal ganglia or cerebellum were specific for ADHD, unlike hypothesized, since these were not present. Likewise, we found no evidence for cortical thickness abnormalities in either of the diagnostic groups, in contrast with previous studies (18). The absence of these abnormalities may be related to the mean age of our sample (16 years) which is relatively old compared with other studies (38). Especially for cortical thickness, the abnormalities seem to normalize with age (39,40). For the basal ganglia specifically, our sample with ADHD may have outgrown their deficits, as suggested in an extensive review that reported that adults with ADHD no longer show those abnormalities (2,41).

Our second hypothesis, that abnormalities in the amygdala and the insula would be driven by ODD rather than by ADHD was not confirmed. A possible explanation is that previously reported abnormalities in amygdala and insula in ADHD+ODD groups are driven by the presence of comorbid CD, a comorbid condition which was absent in our sample. This suggestion is supported by the fact that in

previous studies that showed an association between abnormalities in the amygdala and the insula and ODD/CD, only mixed samples of individuals with ODD and/or CD, rather than individuals with ODD-only, were assessed (15,42). Thus, since ODD has frequently been reported as a milder form of CD, and possibly acts as a precursor for CD, it may be possible that these striatal structures may not be affected in ODD (43).

We found no support for the maturational delay hypothesis in terms of volume or cortical thickness. Although our sample was on average relatively old compared to earlier studies on brain development in ADHD, the age range was large enough to be able to detect possible developmental differences. Since the maturational delay seems most prominent in late childhood (7-13 years) and our sample ranged up to 29 years, a small effect of age may have been missed. Therefore, we re-analyzed our data in an age-restricted subsample (7-13 years), with similar results (data available with first author). It needs to be acknowledged that the cross-sectional design of our study limits the interpretability of the developmental results, and a longitudinal design would be required to specifically test the maturational delay hypothesis. Nevertheless, our findings are based on a large, well-defined sample following strict inclusion criteria, and are in line with a recent longitudinal study including a large sample of children with ADHD (44). This suggests that maybe the maturational delay hypothesis holds true for a specific subset of individuals with ADHD, but not all.

Our study has some important strengths, such as the large sample and well-defined groups, but there are also some limitations. Firstly, it would have been valuable to also have an ODD-only group, to investigate whether the stronger abnormalities in the comorbid group are indeed related to ODD, or rather to an interaction between ADHD and ODD. Secondly, even though we statistically controlled for effects of age, gender, and IQ, this is not the same as investigating matched groups. It is therefore possible that we missed small effects of subtle neuroanatomical abnormalities. Thirdly, most previous studies in ADHD used voxel-based morphometry (VBM) approaches, while the current study used a

surface-based morphometry (SBM) approach. This was preferred because SBM has been shown to be most robust across different scanners (45). Although SBM and VBM are different approaches, results in terms of cortical volume from both approaches are highly correlated (46). Furthermore, our voxel-wise results were non-significant. Although the approaches differ substantially, both have their merits and they may be seen as complementary (47). Additionally, our findings did largely overlap with the uncorrected voxel-wise results, indicating that abnormalities were distributed rather than focal. Fourthly, the prevalence of comorbid ODD in our sample is relatively low (22%) compared to other studies, but is in line with the idea that comorbid problems in ADHD emerge early in childhood and remit during adolescence (48), and is a consequence of the strict inclusion criteria applied (e.g. no mood/anxiety disorders, no CD). However, ODD severity was still comparable with other studies (mean 5.2, range 4-8 symptoms).

Taken together, our study showed that both individuals with ADHD-only and ADHD+ODD show volumetric reductions in total gray matter and in brain areas crucial for attention, (working) memory and decision making, but do not show abnormalities in similar brain areas in cortical thickness. Given the absence of cortical thickness abnormalities, the observed volumetric reductions are most likely driven by reduced surface area development of the involved structures (49). Post-hoc analyses confirmed reduced surface area for the diagnostic groups for the majority (79%) of structures for which volumetric reductions were observed (S3). This is in line with a study that showed regional variation in the contribution of thickness and surface area to volumetric differences (50). For the other areas it may be that small abnormalities in cortical thickness and surface area together resulted in the observed volumetric reductions, but this remains speculative. Furthermore, the volumetric reductions in the frontal lobes were largest in the ADHD+ODD group, possibly underlying the larger impairments in neurocognitive functions commonly observed in this comorbid group (24,51,52). Thus, individuals with ADHD+ODD seem to face a double burden and show an accumulation of the deficits associated with

each of the separate disorders. Moreover, there were disorder-specific abnormalities for the ADHD+ODD group not only in the frontal regions, but also in the precuneus and the middle temporal gyrus, in line with neurocognitive findings of impairments in social skills in individuals with (comorbid) ODD.

Declaration of interest

Dr. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Lundbeck, Medice, Shire, Roche, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties.

Dr. Franke received an educational speaking fee from Merz.

Dr. Hoekstra has been in the past 3 years a consultant to / member of advisory board for Shire.

Dr. Oosterlaan has received unrestricted investigator initiated research grants from Shire pharmaceuticals.

Dr. Faraone received income, travel expenses and/or research support from and/or has been on an Advisory Board for Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences and research support from the National Institutes of Health (NIH), the K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Bergen, Norway and the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n°602805 and NIMH grants R13MH059126 and R01MH094469. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by: Shire, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier, ADHD: Non-Pharmacologic Treatments.

All other authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

This work was supported by NIH Grant R01MH62873, NWO Large Investment Grant 1750102007010 and

an NWO Brain & Cognition grant (056-24-011), the European Union 7th Framework programs AGGRESSOTYPE (602805) and MATRICS (603016), and by grants from Radboud University Medical Center, University Medical Center Groningen and Accare, and Vrije Universiteit Amsterdam. Barbara Franke is supported by a Vici grant from the Netherlands Organization for Scientific Research (NOW; grant number 016-310-669).

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Figure captions

Figure 1

Title: Overall volumetric group differences between the three groups, based on whole brain voxel-wise analyses.

Legend: Lateral (top) and sagittal (bottom) view of the left (left) and right (right) hemispheres. Colored areas indicate clusters exhibiting overall group differences in cortical volume for all three groups (controls, ADHD-only, ADHD+ODD). Results are uncorrected for multiple comparisons, $p < .0001$. Yellow indicates the center of gravity for the clusters. Dark gray = sulci; light gray = gyri.

Figure 2

Title: Stepwise volumetric reductions

Legend: ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, TDC = Typically Developing Controls. Volumes are provided in milliliters (ml), error bars represent 95%-confidence intervals.

* $p < .05$, ** $p < .01$, *** $p < .001$

Figure 3

Title: Disorder-specific volumetric reductions

Legend: ADHD = Attention-Deficit/Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, TDC = Typically Developing Controls. Volumes are provided in milliliters (ml), error bars represent 95%-confidence intervals.

* $p < .05$, ** $p < .01$, *** $p < .001$, *ns* = not significant

Table 1

Group Characteristics

	ADHD+ODD		ADHD-only		TDC		Group comparisons
	(n = 67)		*(n = 243)*		*(n = 233)*		
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age (years)	16.3	3.2	17.0	3.5	16.6	3.6	ns
range (years)	8 - 22		7 - 25		7 - 29		
IQ	98.0	11.2	96.9	16.1	105.9	13.9	ADHD+ODD < TDC ***, ADHD-only < TDC ***; ADHD+ODD = ADHD-only
Gender (% Male)	66		68		55		ADHD+ODD > TDC *; ADHD-only > TDC ***; ADHD+ODD = ADHD-only
Scan site (% Amsterdam)	42		42		64		ADHD+ODD < TDC **; ADHD-only < TDC ***; ADHD+ODD = ADHD-only
Medication use[a] (mg)	58373	49668	61848	57795	-	-	ns
ADHD total symptoms[b]	14.3	2.5	12.9	3.0	1.3	2.4	ADHD+ODD > ADHD-only ***; ADHD+ODD > TDC ***; ADHD-only > TDC ***
Hyperactive symptoms[b]	6.6	2.1	5.8	2.4	0.5	1.2	ADHD+ODD > ADHD-only *; ADHD+ODD > TDC ***; ADHD-only > TDC ***
Inattentive symptoms[b]	7.8	1.2	7.1	1.8	0.8	1.6	ADHD+ODD > ADHD-only ***; ADHD+ODD > TDC ***; ADHD-only > TDC ***
ODD symptoms[b]	5.1	1.2	1.0	1.8	0.0	0.5	ADHD+ODD > ADHD-only ***; ADHD+ODD > TDC ***; ADHD-only > TDC ***

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; ODD = Oppositional Defiant Disorder; TDC = Typically Developing Controls

[a] Cumulative stimulation medication intake, calculated by multiplying treatment duration and mean daily dose, corrected for age (see Schweren et al. 2015)

[b] As measured using the combination of K-SADS-PL and Conners scales Total, Inattentive, Hyperactive/Impulsive

** p < .05, ** p < .01, *** p < .001*

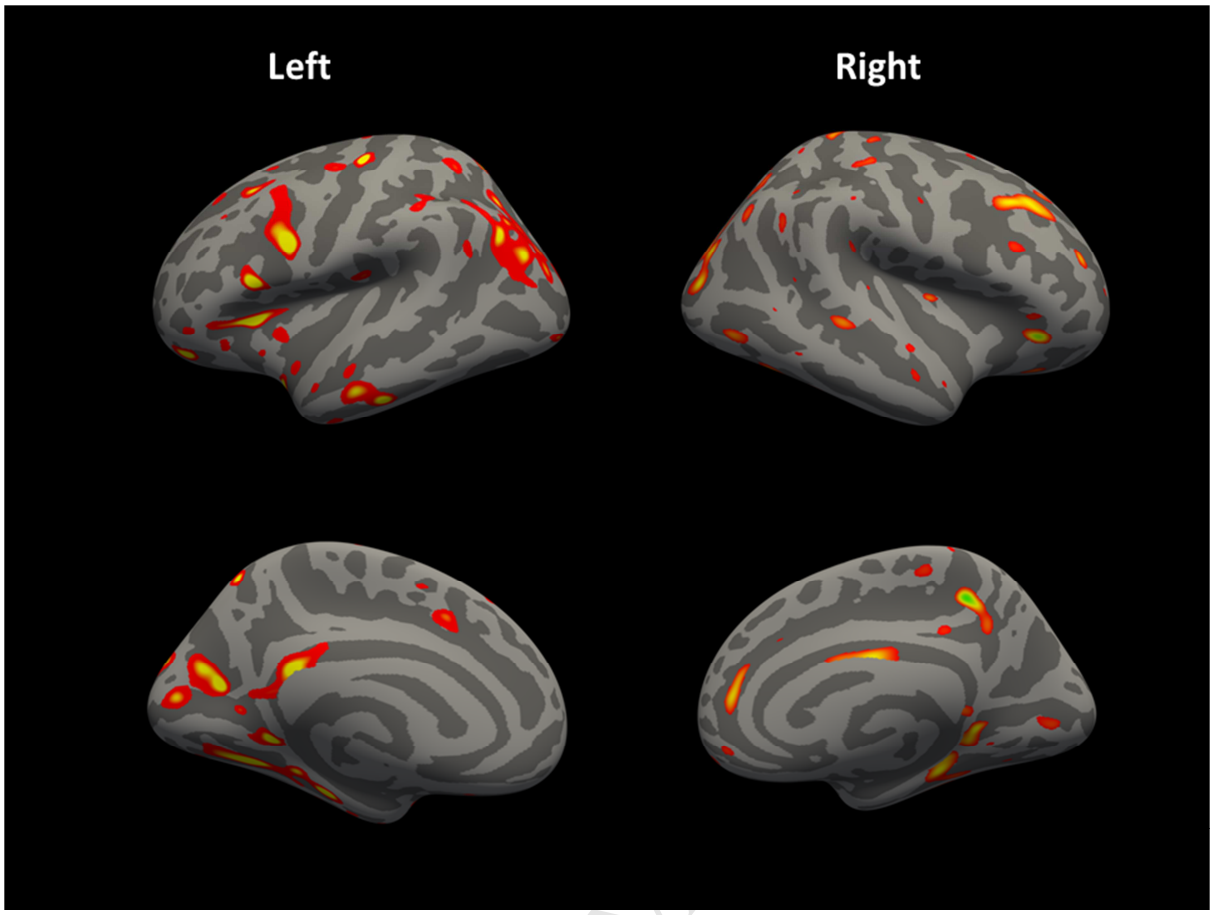
Table 2

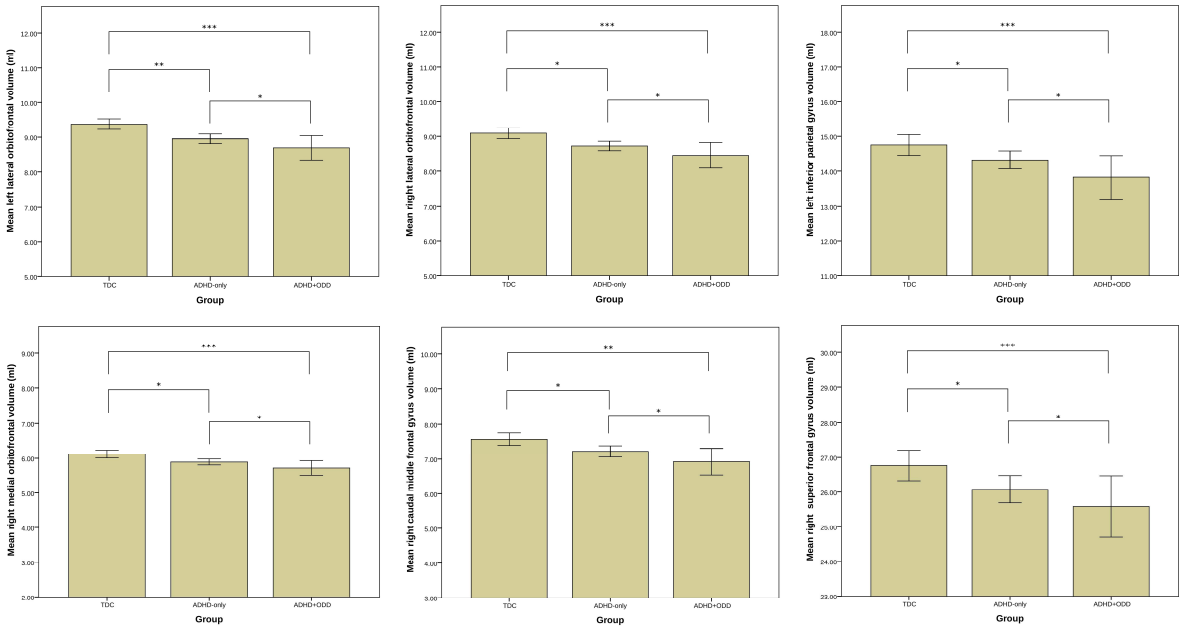
Results of Diagnostic Group Comparisons Accounting for ADHD Symptom Severity - Volume

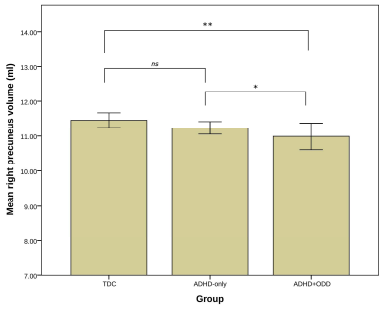
Structure	Lateralisation	ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		Main effect of group	Post-hoc group comparisons
		M (ml)	*SD (ml)*	*M (ml)*	*SD (ml)*		
Linear volumetric reduction							
Lateral orbitofrontal	Left	8.69	1.43	8.95	1.09	F (1,301) = 5.24 *	ADHD-only > ADHD+ODD
	Right	8.45	1.51	8.72	1.06	F (1,300) = 5.53 *	ADHD-only > ADHD+ODD
Medial orbitofrontal	Right	5.72	0.87	5.89	0.69	F (1,297) = 6.63 *	ADHD-only > ADHD+ODD
Caudal middle frontal	Right	6.93	1.57	7.22	1.28	F (1,295) = 3.38	ns
Inferior parietal gyrus	Left	13.83	2.51	14.32	2.04	F (1,299 = 6.19 *	ADHD-only > ADHD+ODD
Superior frontal gyrus	Right	25.58	3.63	26.08	3.11	F (1,295) = 4.38 *	ADHD-only > ADHD+ODD
Disorder specificity							
Rostral middle frontal	Left	18.89	3.14	19.32	2.80	F (1,294) = 7.69 **	ADHD-only > ADHD+ODD
Medial orbitofrontal	Left	5.58	0.93	5.83	0.76	F (1,301) = 7.04 **	ADHD-only > ADHD+ODD
Precuneus	Right	10.99	1.56	11.23	1.44	F (1,286) = 4.57 *	ADHD-only > ADHD+ODD
Pars triangularis	Left	3.99	0.61	4.20	0.70	F (1,300) = 6.46 *	ADHD-only > ADHD+ODD
Middle temporal gyrus	Left	12.32	1.97	12.68	1.84	F (1,301) = 4.09 *	ADHD-only > ADHD+ODD

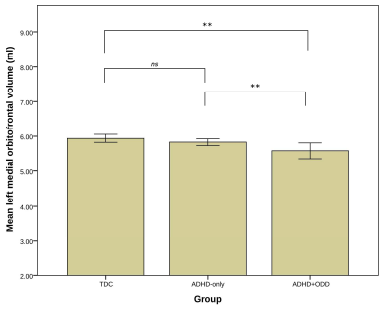
Note: ADHD = Attention-Deficit/Hyperactivity Disorder; ODD = Oppositional Defiant Disorder

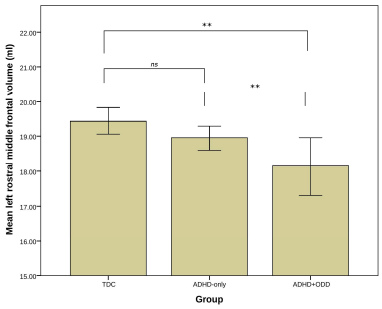
* p < .05, ** p < .01 , ***p < .001

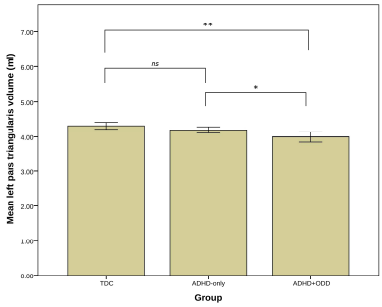


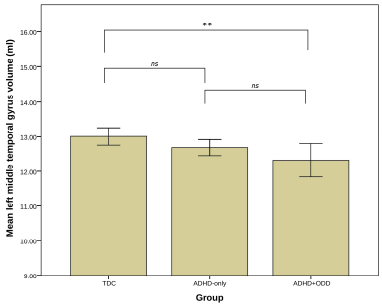












Structural Brain Abnormalities of Attention-Deficit/Hyperactivity Disorder with Oppositional Defiant Disorder

Supplemental Information

Supplemental Methods

The cohort *(adapted from (1))*

Original IMAGE cohort (2003–2006)

Participants for NeuroIMAGE were selected from the Dutch part of the International Multicenter ADHD Genetics (IMAGE) study, conducted between 2003 and 2006. In the Dutch part of IMAGE 365, families with at least one child with combined subtype ADHD and at least one biological sibling (regardless of ADHD diagnosis) were recruited, in addition to 148 control families with at least one child, with no formal or suspected ADHD diagnosis in any of the first degree family members. Inclusion criteria for the IMAGE study were: participants had to be between 5 and 30 years, of European Caucasian descent, have an IQ >70, and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders (such as Fragile X syndrome or Down syndrome).

NeuroIMAGE (2009–2012)

For NeuroIMAGE, all family members, including those who did not participate in IMAGE, were invited for follow-up measurement and (re)assessed between 2009 and 2012. The time between the IMAGE and NeuroIMAGE measurements ranged between 3.5 and 8.9 years (overall M = 5.9 years, SD = 0.74). Additionally, children with ADHD (foremost girls) and healthy control boys were newly recruited to balance the distribution of gender and age between the ADHD and healthy control groups in NeuroIMAGE. Inclusion criteria were largely consistent with the IMAGE study, except that we now

allowed inclusion of children with any subtype ADHD rather than the combined subtype only.

Including the newly recruited families, the complete NeuroIMAGE cohort comprised testing of more than 1,000 children and approximately 850 tested parents. Retention rate from the original IMAGE study was high (79%). The most important reasons for drop-out were being too busy, family problems, and time consumption of the study.

Diagnostic assessment

Diagnostic assessment of all participants included the comprehensive assessment of ADHD and ODD symptoms. To determine ADHD and ODD diagnoses, participants were assessed using the Dutch translation of the Kiddie–Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL; 2). In addition, each child was assessed with a teacher rating (Conners' Teacher Rating Scale–Revised: Long version [CTRS-R:L], applied for children <18 years; 3) or a self-report questionnaire (Conners' Adult ADHD Rating Scales–Self-Report:Long Version [CAARS-S:L], applied for children ≥18 years; 4). The CTRS-R:L assesses both ADHD and ODD symptoms, whereas the CAARS-S:L assesses only ADHD symptoms. For participants using medication, ratings were done of children's functioning off medication. For ADHD, a diagnostic algorithm was applied to combine symptom counts on the K-SADS and CTRS-R:L (for participants <18 years) or CAARS-S:L (for participants ≥18), both providing operational definitions of ADHD defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (5). Participants with ADHD were required to obtain a combined symptom count of ≥6 symptoms of hyperactive/impulsive behavior and/or inattentive behavior, provided they (a) met the DSM-IV criteria for pervasiveness and impact of the disorder (K-SADS), (b) showed an age of onset before 12 (K-SADS), and (c) received a T ≥ 63 on at least one of the DSM ADHD scales (Total, Inattentive behavior, Hyperactive/ Impulsive behavior) on either one of the Conners' questionnaires. Likewise, for ODD, a diagnostic algorithm was applied to combine symptom counts on the K-SADS and

CTRS-R:L (for participants <18 years), both providing operational definitions of ODD defined by the DSM-IV (5). Participants with ODD were required to obtain a combined symptom count of ≥4 symptoms of oppositional behavior, provided they (a) met the DSM-IV criteria for pervasiveness and impact of the disorder (K-SADS), and (b) received a T ≥63 on the DSM Oppositional behavior scale of the CTRS-R:L.

The MRI assessment

Quality assurance procedures, *(adapted from (6))*

For MRI data, several data checks to assess the quality of the collected scans were implemented. Since head movement during MRI scans can greatly impact the quality of the data collected, several steps to minimize movement during scanning and to assess data quality afterwards were taken. Before the MRI session, all participants were trained in a mock scanner to keep their head still while images were acquired. During the structural scans, participants were offered to watch a short movie or to listen to their favorite music, thereby distracting them from scanning, while helping them to stay still. When participants moved excessively (e.g. seen by moving feet), feedback was given and the participant was encouraged to stay still for the next scan. Given the importance of the anatomical scan for processing the other scan types that were also assessed in the NeuroIMAGE study (i.e., to allow correct normalization to a common space), we administered the T1 anatomical scan twice during the MRI session.

Furthermore, a quantitative between-group comparison of head movement during functional MRI scans was made. To this end, three head rotation (degrees) and three translation parameters (millimetres) were calculated using SPM8 software (Wellcome Trust Centre for Neuroimaging, UCL). Rotation parameters were converted to distances (in millimetres). By taking the summed absolute image-to-image displacement per parameter and adding these up, a summary score of the total movement over the time series per participant was constructed. Peaks of these distributions were

slightly shifted between ADHD cases and controls, suggesting that the ADHD cases moved a bit more during scanning. However, for all sequences, we observed an almost complete overlap of distributions indicating that within-group variance was much larger than between-group variance. This is also illustrated by the computed Cohen's effect sizes that, varying between 0.10 and 0.51, appear to be small to moderate. We concluded from these observations that movement is not very likely to confound our case–control comparisons and we therefore decided to deal with movement in a standard fashion (i.e., statistical correction using realignment parameters in 1st/2nd level analysis, exclusion of extreme movers/outliers, post hoc analysis whether movement does confound a specific analysis).

For the T1 anatomical scans, two independent raters evaluated quality of both scans on a 4-point scale (1 = good; 2 = useable; 3 = poor; 4 = very poor). Consistency between both raters was sufficient to good (ICC: 0.59) and the evaluated quality of the scans was good: from 1,559 scans, only 105 (6.7%) were rated other than good or usable by one of the raters, leaving 767 (96%) participants with at least one useful structural scan. When two good scans were available volumetric characteristics were calculated based on the average of these two, otherwise only the best scan was chosen. Only scans with no or mild distortions were included. For further quality check after the FreeSurfer procedures were completed, the following reconstructions were subjected to visual inspection to detect regions of "flattened" or "spiky" surface and surface wholes: 1) twenty percent (randomly selected) of all reconstructions; 2) all reconstructions based on a structural scan with mild distortions. Reconstructions that did not meet quality criteria were excluded from the analyses; no manual edits were made.

Finally, to evaluate potential site effects within our experimental design, we selected one measure of interest for each imaging modality. For the anatomical scan, we selected relative grey matter volume (grey matter divided by the total brain volume as estimated by SPM). As expected, differences between sites could be observed in the distribution of all measurements. However, all measures exhibited large overlap [Cohen's d was in the range between (±) 0.12 and 0.76, with a mean

around 0.50] between sites, suggesting that between-subject variability within site outweighed any systematic between-site differences. Importantly, compared to the effect on raw image quality, site had a considerably smaller effect on most derived measures indicating that in our study site effects are likely to play a less important role when answering experimental questions.

Scanner parameters

Whole-brain high-resolution T1-weighted anatomical images were acquired in the sagittal plane: magnetization-prepared rapid acquisition gradient echo (MP-RAGE), echo time (TE)=2.95 ms, repetition time (TR)=2730 ms, inversion time (TI)=1000 ms, flip angle (FA)=7°, using generalized auto-calibrating partially parallel acquisition (GRAPPA) with 176 sagittal slices, voxel size 1x1x1 mm^3, and acquisition matrix 256x256.

Assessed anatomical areas

Global and more specific volumetric and cortical thickness characteristics were calculated from Freesurfer Parcellations and Segmentations, the latter with the use of the Desikan-Killiany atlas (7).

<u>Volumetric global measures</u>

- Total intracranial volume (covariate)
- Total gray matter volume
- Corpus Callosum
- Total cortical volume
- Subcortical gray matter
- Brain stem

<u>Volumetric cortical measures:</u>

- Corpus Callosum
- Parahippocampus
- Insula
- Inferior parietal gyrus

- Superior parietal gyrus
- Middle temporal gyrus
- Transverse temporal gyrus
- Caudal middle frontal gyrus
- Pars orbitalis
- Pars opercularis
- Lateral orbitofrontal gyrus
- Frontal pole
- Rostral anterior cingulate cortex
- Lateral occipital gyrus
- Precuneus
- Fusiform gyrus
- Precentral gyrus
- Postcentral gyrus
- Cerebellum (white matter)
- Inferior temporal gyrus
- Superior temporal gyrus
- Temporal pole
- Rostral middle frontal gyrus
- Pars triangularis
- Medial orbitofrontal gyrus
- Superior frontal gyrus
- Caudal anterior cingulate cortex
- Posterior cingulate
- Cuneus
- Entorhinal
- Isthmus
- Paracentral gyrus
- Supramarginal gyrus
- Cerebellum (cortex)

<u>Volumetric subcortical measures:</u>

- Accumbens
- Caudate
- Globus pallidus
- Thalamus
- Amygdala
- Hippocampus
- Putamen

Cortical thickness measures:

- Insula
- Inferior parietal gyrus
- Inferior temporal gyrus
- Superior temporal gyrus
- Temporal pole
- Caudal middle frontal gyrus
- Pars orbitalis
- Pars opercularis
- Lateral orbitofrontal gyrus
- Parahippocampus
- Superior parietal gyrus
- Middle temporal gyrus
- Transverse temporal gyrus
- Superior frontal gyrus
- Rostral middle frontal gyrus
- Pars triangularis
- Medial orbitofrontal gyrus

Supplemental Tables

Table S1. Results of Whole Brain Group Comparisons - Volume

Structure	Lateralisation	ADHD+ODD (*n* = 67) *M (ml)*	ADHD+ODD (*n* = 67) *SD (ml)*	ADHD-only (*n* = 243) *M (ml)*	ADHD-only (*n* = 243) *SD (ml)*	TDC (*n* = 233) *M (ml)*	TDC (*n* = 233) *SD (ml)*	Main effect of group	Post-hoc group comparisons for FDR-corrected results
Subcortical Structures									
Subcortical gray volume		61.51	5.86	61.92	5.42	62.06	5.22	F (2,464) = 0.83	ns
Accumbens	Left	0.66	0.13	0.66	0.11	0.68	0.12	F (2,457) = 0.68	ns
Accumbens	Right	0.67	0.11	0.65	0.10	0.67	0.10	F (2,452) = 0.69	ns
Amygdala	Left	1.50	0.20	1.51	0.21	1.55	0.20	F (2,444) = 2.28	ns
Amygdala	Right	1.52	0.21	1.51	0.21	1.55	0.20	F (2,447) = 1.36	ns
Caudate	Left	3.98	0.57	4.08	0.53	4.10	0.52	F (2,444) = 1.74	ns
Caudate	Right	4.29	0.59	4.36	0.54	4.41	0.54	F (2,455) = 1.48	ns
Hippocampus	Left	4.03	0.48	4.04	0.41	4.08	0.39	F (2,449) = 1.06	ns
Hippocampus	Right	4.03	0.47	4.01	0.40	4.06	0.38	F (2,444) = 1.34	ns
Globus pallidus	Left	1.84	0.28	1.87	0.26	1.88	0.30	F (2,446) = 1.47	ns
Globus pallidus	Right	1.79	0.23	1.81	0.22	1.81	0.22	F (2,460) = 0.67	ns
Putamen	Left	6.36	0.80	6.28	0.70	6.30	0.77	F (2,467) = 0.14	ns
Putamen	Right	6.22	0.66	6.11	0.66	6.15	0.70	F (2,480) = 0.41	ns
Thalamus	Left	8.02	0.94	8.21	0.89	8.11	0.87	F (2,454) = 1.60	ns
Thalamus	Right	7.40	0.77	7.58	0.73	7.50	0.73	F (2,430) = 2.46	ns
Brain Stem		21.04	2.77	21.33	2.51	20.88	2.33	F (2,460) = 0.27	ns
Cortical Structures									
Total cortical volume		527.37	66.38	532.71	54.03	545.63	60.13	F (2,441) = 6.75 ** †	TDC > ADHD-only, ADHD+ODD
Total gray matter volume		697.75	78.84	702.81	63.34	715.62	72.13	F (2,443) = 7.09 ** †	TDC > ADHD-only, ADHD+ODD
Corpus Callosum		2.91	0.55	3.04	0.50	2.96	0.46	F (2,473) = 2.37	ns
Insula	Left	7.11	1.02	7.29	0.90	7.39	1.01	F (2,456) = 2.75	ns
Insula	Right	7.32	1.14	7.46	0.96	7.50	0.96	F (2,431) = 1.84	ns
Parahippocampus	Left	2.45	0.46	2.42	0.38	2.51	0.36	F (2,416) = 1.96	ns
Parahippocampus	Right	2.20	0.43	2.24	0.33	2.34	0.36	F (2,421) = 7.18 *** †	TDC > ADHD-only, ADHD+ODD
Inferior parietal gyrus	Left	13.83	2.51	14.32	2.04	14.75	2.31	F (2,417) = 7.89 *** †	TDC > ADHD-only > ADHD+ODD
Inferior parietal gyrus	Right	17.40	2.92	17.33	2.55	17.80	2.64	F (2,409) = 4.24 ** †	TDC > ADHD-only, ADHD+ODD
Superior parietal gyrus	Left	14.10	1.68	14.26	1.85	14.40	2.10	F (2,442) = 2.58	ns
Superior parietal gyrus	Right	14.31	1.58	14.31	1.76	14.41	2.07	F (2,427) = 1.66	ns
Inferior temporal gyrus	Left	12.38	2.25	12.91	1.93	13.03	1.91	F (2,434) = 3.44 *	ns
Inferior temporal gyrus	Right	12.27	2.16	12.59	1.97	12.65	2.00	F (2,445) = 2.18	ns

Structure	Lateralisation	ADHD+ODD (*n* = 67) *M (ml)*	ADHD+ODD (*n* = 67) *SD (ml)*	ADHD-only (*n* = 243) *M (ml)*	ADHD-only (*n* = 243) *SD (ml)*	TDC (*n* = 233) *M (ml)*	TDC (*n* = 233) *SD (ml)*	Main effect of group	Post-hoc group comparisons for FDR-corrected results
Middle temporal gyrus	Left	12.32	1.97	12.68	1.84	13.00	1.96	F (2,427) = 4.63 ** †	TDC > ADHD+ODD; TDC = ADHD-only; ADHD-only = ADHD+ODD
Middle temporal gyrus	Right	13.81	2.24	14.08	1.76	14.31	1.95	F (2,405) = 2.55	ns
Superior temporal gyrus	Left	13.99	2.45	13.98	1.78	14.05	1.93	F (2,434) = 0.39	ns
Superior temporal gyrus	Right	13.18	2.22	13.29	1.64	13.56	1.76	F (2,454) = 1.59	ns
Transverse temporal gyrus	Left	1.33	0.25	1.31	0.25	1.33	0.27	F (2,436) = 0.11	ns
Transverse temporal gyrus	Right	1.00	0.25	1.03	0.22	1.04	0.21	F (2,433) = 0.86	ns
Temporal pole	Left	2.55	0.39	2.57	0.40	2.65	0.37	F (2,437) = 2.33	ns
Temporal pole	Right	2.25	0.45	2.31	0.39	2.40	0.39	F (2,424) = 3.53 *	ns
Pars orbitalis	Left	2.54	0.47	2.57	0.39	2.71	0.43	F (2,427) = 3.14 *	ns
Pars orbitalis	Right	3.07	0.54	3.11	0.44	3.25	0.52	F (2,429) = 4.00 *	ns
Pars triangularis	Left	3.99	0.61	4.20	0.70	4.31	0.77	F (2,384) = 5.05 ** †	TDC, ADHD-only > ADHD+ODD
Pars triangularis	Right	4.79	0.94	4.92	0.79	5.09	0.92	F (2,432) = 3.05 *	ns
Pars opercularis	Left	5.76	1.08	5.83	0.90	5.92	0.95	F (2,391) = 0.26	ns
Pars opercularis	Right	4.71	0.82	4.77	0.84	4.92	0.86	F (2,446) = 1.49	ns
Caudal middle frontal	Left	7.60	1.41	7.71	1.39	8.14	1.40	F (2,434) = 6.09 ** †	TDC > ADHD+ODD, ADHD-only
Caudal middle frontal	Right	6.93	1.57	7.22	1.28	7.58	1.39	F (2,436) = 6.29 ** †	TDC > ADHD-only > ADHD+ODD
Rostral middle frontal	Left	18.14	3.33	18.95	2.80	19.44	3.02	F (2,435) = 6.35 ** †	TDC, ADHD-only > ADHD+ODD
Rostral middle frontal	Right	18.89	3.14	19.32	2.80	20.01	3.08	F (2,430) = 5.34 ** †	TDC > ADHD+ODD, ADHD-only
Medial orbitofrontal	Left	5.58	0.93	5.83	0.76	5.94	0.89	F (2,442) = 5.49 ** †	TDC, ADHD-only > ADHD+ODD
Medial orbitofrontal	Right	5.72	0.87	5.89	0.69	6.12	0.89	F (2,458) = 8.45 *** †	TDC > ADHD-only > ADHD+ODD
Lateral orbitofrontal	Left	8.69	1.43	8.95	1.09	9.38	1.19	F (2,448) = 10.51 *** †	TDC > ADHD-only > ADHD+ODD
Lateral orbitofrontal	Right	8.45	1.51	8.72	1.06	9.09	1.22	F (2,443) = 8.25 *** †	TDC > ADHD-only > ADHD+ODD
Superior frontal gyrus	Left	26.87	3.96	26.93	3.13	27.65	3.50	F (2,440) = 3.86 *	ns
Superior frontal gyrus	Right	25.58	3.63	26.08	3.11	26.77	3.41	F (2,447) = 6.37 ** †	TDC > ADHD-only > ADHD+ODD
Frontal pole	Left	0.94	0.20	0.92	0.18	0.97	0.20	F (2,415) = 1.74	ns
Frontal pole	Right	1.26	0.28	1.25	0.24	1.30	0.28	F (2,443) = 1.60	ns
Caudal anterior cingulate cortex	Left	2.10	0.50	2.13	0.52	2.26	0.58	F (2,425) = 2.00	ns
Caudal anterior cingulate cortex	Right	2.46	0.59	2.44	0.58	2.50	0.65	F (2,424) = 0.04	ns
Rostral anterior cingulate cortex	Left	3.00	0.62	3.04	0.53	3.22	0.60	F (2,440) = 4.04 *	ns
Rostral anterior cingulate cortex	Right	2.28	0.54	2.38	0.43	2.42	0.51	F (2,430) = 1.46	ns
Posterior cingulate	Left	3.54	0.67	3.63	0.60	3.71	0.61	F (2,421) = 2.78	ns
Posterior cingulate	Right	3.53	0.66	3.59	0.56	3.64	0.61	F (2,416) = 1.92	ns
Lateral occipital gyrus	Left	12.05	1.79	12.14	1.61	12.43	1.78	F (2,440) = 4.82 ** †	TDC > ADHD-only, ADHD+ODD
Lateral occipital gyrus	Right	12.41	1.77	12.44	1.66	12.56	1.91	F (2,445) = 1.52	ns
Cuneus	Left	3.13	0.47	3.08	0.49	3.10	0.54	F (2,447) = 0.75	ns
Cuneus	Right	3.27	0.54	3.36	0.50	3.37	0.61	F (2,442) = 3.02 *	ns
Precuneus	Left	10.71	1.49	10.77	1.39	11.00	1.57	F (2,434) = 4.19 *	ns
Precuneus	Right	10.99	1.56	11.23	1.44	11.46	1.64	F (2,447) = 5.34 ** †	TDC, ADHD-only > ADHD+ODD

Structure	Lateralisation	ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		TDC (*n* = 233)		Main effect of group	Post-hoc group comparisons for FDR-corrected results
		M (ml)	*SD (ml)*	*M (ml)*	*SD (ml)*	*M (ml)*	*SD (ml)*		
Entorhinal	Left	1.90	0.43	1.96	0.42	1.98	0.36	F (2,403) = 2.60	ns
Entorhinal	Right	1.77	0.47	1.81	0.43	1.81	0.34	F (2,389) = 1.06	ns
Fusiform gyrus	Left	11.14	1.87	11.11	1.50	11.40	1.80	F (2,441) = 3.11 *	ns
Fusiform gyrus	Right	10.70	1.84	10.94	1.40	11.02	1.66	F (2,436) = 2.98 *	ns
Isthmus	Left	2.91	0.54	2.95	0.50	3.02	0.54	F (2,416) = 5.13 ** †	TDC > ADHD-only, ADHD+ODD
Isthmus	Right	2.63	0.41	2.71	0.45	2.81	0.51	F (2,410) = 7.71 *** †	TDC > ADHD-only, ADHD+ODD
Precentral gyrus	Left	14.42	1.72	14.69	1.73	15.00	1.91	F (2,448) = 5.56 ** †	TDC > ADHD-only, ADHD+ODD
Precentral gyrus	Right	14.54	1.91	14.72	1.68	14.99	1.85	F (2,436) = 3.77 *	ns
Paracentral gyrus	Left	3.76	0.62	3.74	0.64	3.85	0.65	F (2,430) = 2.46	ns
Paracentral gyrus	Right	4.21	0.80	4.20	0.72	4.29	0.73	F (2,429) = 1.86	ns
Postcentral gyrus	Left	10.70	1.75	10.72	1.36	10.73	1.50	F (2,432) = 0.66	ns
Postcentral gyrus	Right	10.04	1.47	10.09	1.51	10.17	1.52	F (2,446) = 1.31	ns
Supramarginal gyrus	Left	12.71	1.78	12.79	1.91	12.89	2.06	F (2,434) = 2.14	ns
Supramarginal gyrus	Right	11.92	1.89	12.06	1.84	12.25	1.97	F (2,432) = 2.73	ns
Cerebellum (white matter)	Left	13.60	1.96	13.77	1.80	13.67	1.66	F (2,463) = 0.22	ns
Cerebellum (white matter)	Right	13.83	1.93	14.04	1.86	13.92	1.66	F (2,462) = 0.36	ns
Cerebellum (cortex)	Left	54.34	5.99	53.87	5.20	53.71	5.89	F (2,458) = 1.29	ns
Cerebellum (cortex)	Right	55.54	6.68	55.30	5.47	55.26	6.11	F (2,457) = 2.16	ns

ADHD = Attention-Deficit/Hyperactivity Disorder; FDR-correction = False Discovery Rate-correction; ODD = Oppositional Defiant Disorder; TDC = Typically Developing Controls.

Results of the post-hoc group comparisons are only reported for structures that showed significant group comparisons after FDR-correction ($p < .05$).

* $p < .05$, ** $p < .01$, ** *$p < .001$.

† survived FDR-correction ($p < .05$).

Table S2. Results of Whole Brain Group Comparisons - Cortical Thickness

		ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		TDC (*n* = 233)		Main effect of group	Post-hoc group comparisons for FDR-corrected results
Structure	**Lateralisation**	***M (mm)***	***SD (mm)***	***M (mm)***	***SD (mm)***	***M (mm)***	***SD (mm)***		
Mean thickness		2.52	0.12	2.53	0.12	2.54	0.12	F (2,443) = 0.58	ns
Insula	Left	3.03	0.18	3.04	0.15	3.06	0.15	F (2,426) = 1.41	ns
Insula	Right	3.03	0.19	3.06	0.16	3.05	0.16	F (2,437) = 1.28	ns
Parahippocampus	Left	2.62	0.32	2.66	0.32	2.73	0.33	F (2,434) = 2.18	ns
Parahippocampus	Right	2.61	0.30	2.62	0.28	2.69	0.29	F (2,437) = 2.67	ns
Inferior parietal gyrus	Left	2.49	0.19	2.51	0.16	2.51	0.16	F (2,422) = 2.62	ns
Inferior parietal gyrus	Right	2.53	0.17	2.57	0.16	2.57	0.16	F (2,434) = 4.75 **	ns
Superior parietal gyrus	Left	2.18	0.16	2.20	0.16	2.18	0.15	F (2,418) = 2.10	ns
Superior parietal gyrus	Right	2.16	0.15	2.20	0.15	2.18	0.15	F (2,422) = 4.15 *	ns
Inferior temporal gyrus	Left	2.78	0.21	2.81	0.19	2.83	0.18	F (2,414) = 2.45	ns
Inferior temporal gyrus	Right	2.84	0.18	2.87	0.17	2.88	0.17	F (2,415) = 1.72	ns
Middle temporal gyrus	Left	2.87	0.22	2.89	0.23	2.93	0.21	F (2,419) = 0.50	ns
Middle temporal gyrus	Right	2.89	0.20	2.92	0.20	2.93	0.20	F (2,427) = 0.76	ns
Superior temporal gyrus	Left	2.84	0.21	2.86	0.19	2.88	0.17	F (2,438) = 0.77	ns
Superior temporal gyrus	Right	2.85	0.21	2.87	0.18	2.88	0.17	F (2,426) = 0.82	ns
Transverse temporal gyrus	Left	2.44	0.27	2.43	0.22	2.46	0.24	F (2,431) = 0.41	ns
Transverse temporal gyrus	Right	2.47	0.25	2.45	0.25	2.46	0.22	F (2,433) = 0.02	ns
Temporal pole	Left	3.47	0.30	3.56	0.36	3.59	0.30	F (2,424) = 2.55	ns
Temporal pole	Right	3.51	0.49	3.65	0.38	3.66	0.35	F (2,401) = 3.29 *	ns
Pars orbitalis	Left	2.88	0.25	2.85	0.24	2.90	0.24	F (2,428) = 0.05	ns
Pars orbitalis	Right	2.85	0.24	2.85	0.21	2.85	0.23	F (2,406) = 0.42	ns
Pars triangularis	Left	2.57	0.20	2.59	0.20	2.59	0.18	F (2,434) = 1.60	ns
Pars triangularis	Right	2.56	0.18	2.58	0.18	2.60	0.16	F (2,413) = 1.40	ns
Pars opercularis	Left	2.66	0.19	2.69	0.17	2.69	0.16	F (2,452) = 1.07	ns
Pars opercularis	Right	2.64	0.16	2.69	0.16	2.70	0.17	F (2,429) = 3.23 *	ns
Caudal middle frontal	Left	2.67	0.18	2.67	0.16	2.68	0.14	F (2,419) = 0.52	ns

		ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		TDC (*n* = 233)		Main effect of group	Post-hoc group comparisons for FDR-corrected results
Structure	**Lateralisation**	***M (mm)***	***SD (mm)***	***M (mm)***	***SD (mm)***	***M (mm)***	***SD (mm)***		
Caudal middle frontal	Right	2.65	0.16	2.65	0.16	2.66	0.16	F (2,430) = 0.81	ns
Rostral middle frontal	Left	2.53	0.15	2.52	0.16	2.53	0.15	F (2,438) = 0.49	ns
Rostral middle frontal	Right	2.46	0.13	2.46	0.15	2.46	0.15	F (2,444) = 0.88	ns
Medial orbitofrontal	Left	2.52	0.16	2.54	0.19	2.54	0.18	F (2,404) = 0.62	ns
Medial orbitofrontal	Right	2.48	0.19	2.47	0.19	2.50	0.20	F (2,441) = 0.20	ns
Lateral orbitofrontal	Left	2.73	0.18	2.72	0.16	2.76	0.19	F (2,429) = 1.34	ns
Lateral orbitofrontal	Right	2.65	0.17	2.63	0.19	2.65	0.18	F (2,438) = 0.15	ns
Superior frontal gyrus	Left	2.94	0.15	2.93	0.16	2.94	0.16	F (2,430) = 0.04	ns
Superior frontal gyrus	Right	2.88	0.15	2.88	0.16	2.87	0.15	F (2,438) = 0.09	ns
Frontal pole	Left	3.00	0.33	2.95	0.35	2.98	0.33	F (2,406) = 0.38	ns
Frontal pole	Right	2.95	0.31	2.96	0.31	2.95	0.30	F (2,441) = 1.35	ns
Caudal anterior cingulate cortex	Left	2.65	0.23	2.67	0.25	2.70	0.25	F (2,430) = 0.83	ns
Caudal anterior cingulate cortex	Right	2.55	0.25	2.53	0.22	2.54	0.24	F (2,412) = 0.11	ns
Rostral anterior cingulate cortex	Left	2.85	0.27	2.85	0.25	2.89	0.24	F (2,422) = 0.24	ns
Rostral anterior cingulate cortex	Right	2.73	0.28	2.75	0.23	2.79	0.24	F (2,417) = 0.42	ns
Posterior cingulate	Left	2.58	0.19	2.57	0.17	2.62	0.17	F (2,440) = 5.47 **	ns
Posterior cingulate	Right	2.51	0.17	2.51	0.17	2.52	0.17	F (2,394) = 0.59	ns
Lateral occipital gyrus	Left	2.15	0.14	2.15	0.14	2.15	0.14	F (2,435) = 0.55	ns
Lateral occipital gyrus	Right	2.22	0.14	2.22	0.14	2.22	0.14	F (2,438) = 0.57	ns
Cuneus	Left	1.87	0.15	1.85	0.16	1.84	0.15	F (2,432) = 1.74	ns
Cuneus	Right	1.89	0.14	1.89	0.16	1.88	0.15	F (2,408) = 1.16	ns
Precuneus	Left	2.38	0.17	2.40	0.16	2.40	0.16	F (2,420) = 2.86	ns
Precuneus	Right	2.36	0.14	2.40	0.16	2.40	0.15	F (2,426) = 3.08 *	ns
Entorhinal	Left	3.05	0.41	3.14	0.39	3.22	0.33	F (2,383) = 5.34 **	ns
Entorhinal	Right	3.16	0.40	3.25	0.40	3.32	0.34	F (2,392) = 3.81 *	ns
Fusiform gyrus	Left	2.61	0.18	2.63	0.17	2.67	0.15	F (2,423) = 5.30 **	ns
Fusiform gyrus	Right	2.64	0.20	2.67	0.17	2.71	0.15	F (2,420) = 4.29 *	ns

Structure	Lateralisation	ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		TDC (*n* = 233)		Main effect of group	Post-hoc group comparisons for FDR-corrected results
		M (mm)	*SD (mm)*	*M (mm)*	*SD (mm)*	*M (mm)*	*SD (mm)*		
Isthmus	Left	2.53	0.22	2.55	0.21	2.57	0.24	F (2,455) = 1.92	ns
Isthmus	Right	2.49	0.20	2.47	0.19	2.50	0.19	F (2,430) = 1.64	ns
Precentral gyrus	Left	2.56	0.16	2.57	0.14	2.59	0.13	F (2,436) = 1.46	ns
Precentral gyrus	Right	2.53	0.15	2.54	0.15	2.56	0.15	F (2,430) = 1.16	ns
Paracentral gyrus	Left	2.40	0.17	2.40	0.19	2.41	0.17	F (2,440) = 1.44	ns
Paracentral gyrus	Right	2.38	0.14	2.41	0.17	2.42	0.15	F (2,431) = 0.75 *	ns
Postcentral gyrus	Left	2.09	0.14	2.11	0.14	2.10	0.13	F (2,440) = 1.26	ns
Postcentral gyrus	Right	2.07	0.13	2.09	0.15	2.10	0.14	F (2,436) = 1.97	ns
Supramarginal gyrus	Left	2.61	0.18	2.63	0.16	2.64	0.15	F (2,424) = 2.19	ns
Supramarginal gyrus	Right	2.65	0.19	2.67	0.17	2.69	0.15	F (2,427) = 2.88	ns

ADHD = Attention-Deficit/Hyperactivity Disorder; FDR-correction = False Discovery Rate-correction; ODD = Oppositional Defiant Disorder; TDC = Typically Developing Controls.

Results of the post-hoc group comparisons are only reported for structures that showed significant group comparisons after FDR-correction ($p < .05$).

* $p < .05$, ** $p < .01$.

† survived FDR-correction ($p < .05$).

Table S3. Post-hoc Analyses of Surface Area Characteristics of Structures Showing Volumetric Abnormalities

Structure	Lateralisation	ADHD+ODD (*n* = 67)		ADHD-only (*n* = 243)		TDC (*n* = 233)		Main effect of group	Post-hoc group comparisons
		M (mm^2)	*SD* (mm^2)	*M* (mm^2)	*SD* (mm^2)	*M* (mm^2)	*SD* (mm^2)		
Parahippocampus	Right	714.28	106.51	716.79	101.00	729.65	105.67	F (2,450) = 2.64	ns
Inferior parietal gyrus	Left	4870.93	677.39	4966.53	663.26	5109.43	679.07	F (2,429) = 5.83 **	TDC > ADHD+ODD, ADHD-only
Inferior parietal gyrus	Right	5981.31	817.69	5896.56	760.57	6071.81	806.72	F (2,429) = 5.93 **	TDC > ADHD-only; TDC = ADHD+ODD; ADHD-only = ADHD+ODD
Middle temporal gyrus	Left	3326.15	428.57	3434.45	458.65	3491.09	493.04	F (2,449) = 5.98 **	TDC > ADHD+ODD, ADHD-only
Pars triangularis	Left	1345.75	199.25	1390.21	212.20	1426.13	228.57	F (2,386) = 4.50 *	TDC > ADHD+ODD; TDC = ADHD-only; ADHD-only = ADHD+ODD
Caudal middle frontal	Left	2531.25	408.54	2570.07	436.94	2711.09	428.41	F (2,449) = 6.92 **	TDC > ADHD+ODD, ADHD-only
Caudal middle frontal	Right	2298.13	435.28	2413.07	413.91	2509.83	435.82	F (2,444) = 6.21 **	TDC > ADHD+ODD, ADHD-only
Rostral middle frontal	Left	6100.31	923.03	6416.51	873.77	6545.81	885.02	F (2,435) = 7.27 **	TDC, ADHD-only > ADHD+ODD
Rostral middle frontal	Right	6480.13	956.61	6668.08	900.14	6865.33	918.16	F (2,440) = 5.97 **	TDC > ADHD+ODD, ADHD-only
Medial orbitofrontal	Left	1867.43	290.37	1962.53	258.16	1979.49	250.20	F (2,446) = 5.12 **	TDC, ADHD-only > ADHD+ODD
Medial orbitofrontal	Right	1922.12	239.63	1986.53	231.18	2021.82	234.16	F (2,405) = 5.60 **	TDC > ADHD+ODD; TDC = ADHD-only; ADHD-only = ADHD+ODD
Lateral orbitofrontal	Left	2785.07	414.85	2897.16	325.45	3005.10	324.32	F (2,456) = 10.45 ***	TDC > ADHD-only > ADHD+ODD
Lateral orbitofrontal	Right	2769.00	442.71	2863.33	351.11	2954.58	374.78	F (2,446) = 6.16 **	TDC > ADHD+ODD, ADHD-only
Superior frontal gyrus	Right	7649.43	919.72	7818.95	897.77	8014.12	952.80	F (2,455) = 7.00 **	TDC > ADHD+ODD, ADHD-only
Lateral occipital gyrus	Left	5051.91	569.78	5112.11	575.26	5248.45	626.30	F (2,443) = 6.86 ***	TDC > ADHD-only > ADHD+ODD
Precuneus	Right	4232.60	535.85	4289.26	540.68	4372.78	626.30	F (2,456) = 2.85	ns
Isthmus	Left	1081.99	209.32	1064.12	184.74	1081.94	197.91	F (2,430) = 2.25	ns
Isthmus	Right	954.15	156.87	998	998.18	157.68	161.97	F (2,419) = 4.37 *	TDC, ADHD-only > ADHD+ODD
Precentral gyrus	Left	5115.31	476.40	5147.76	592.10	5196.55	579.88	F (2,450) = 2.64	ns

ADHD = Attention-Deficit/Hyperactivity Disorder; ODD = Oppositional Defiant Disorder; TDC = Typically Developing Controls.

* p < .05, ** p < .01 , ** *p < .001, ns = not significant.

Supplemental Figures

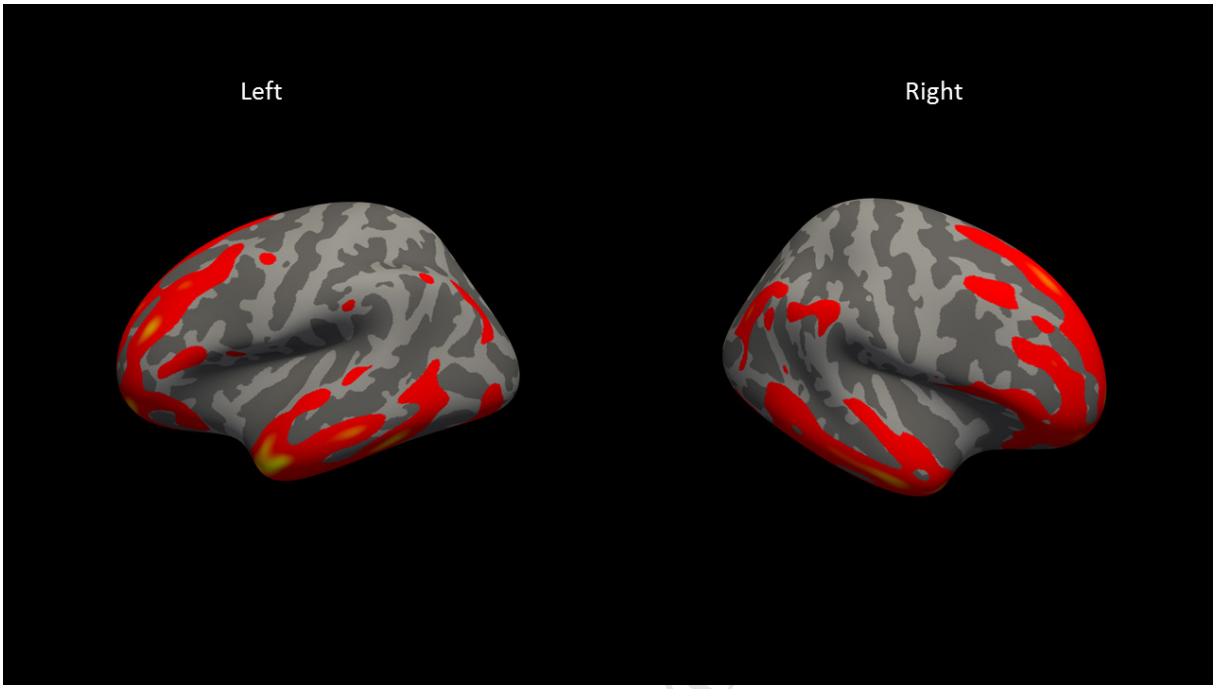


Figure S1. Volumetric group differences between the control group and the ADHD-only group based on whole brain voxel-wise analyses.

Lateral view of the left (left) and right (right) hemispheres. Colored areas indicate clusters exhibiting between-group differences in cortical volume for the control group versus the ADHD-only group comparison. Results are uncorrected for multiple comparisons, $p < .0001$. Yellow indicates the center of gravity for the clusters. Dark gray = sulci; light gray = gyri. *Note.* The Figure is only to illustrate the findings and to give an indication of the distribution of the effects, and is based on a whole brain voxel-wise approach rather than the ROI approach that is described in the manuscript.

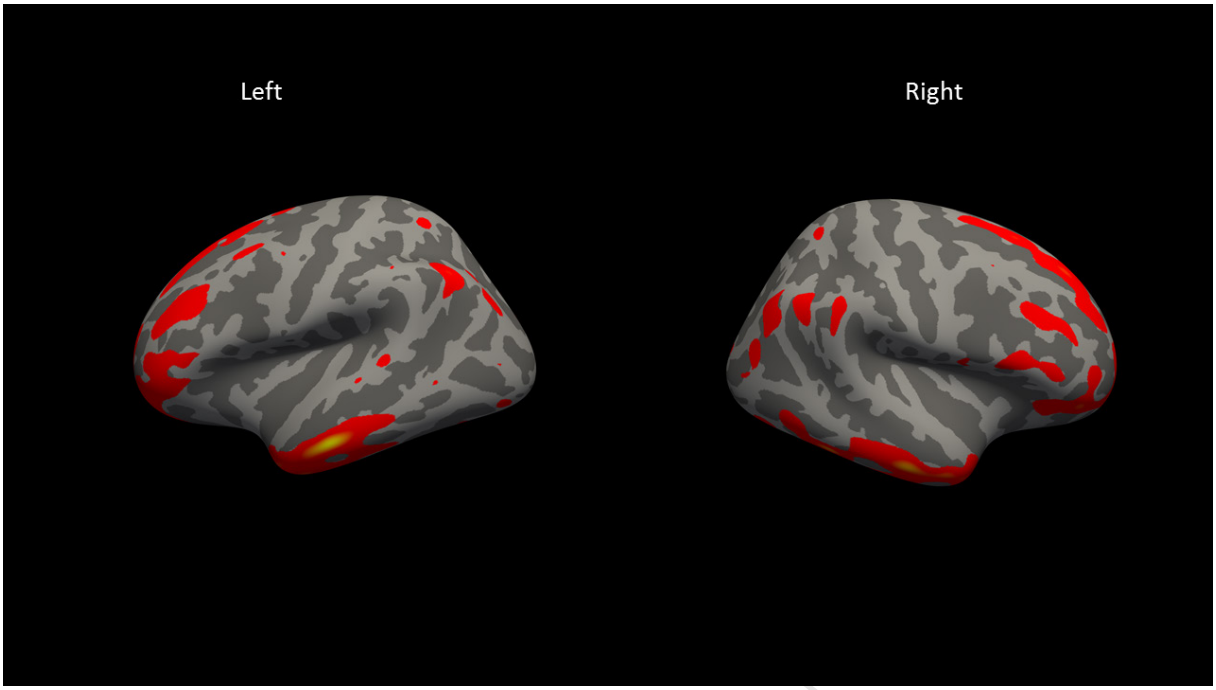


Figure S2. Volumetric group differences between the control group and the ADHD+ODD group based on whole brain voxel-wise analyses.

Lateral view of the left (left) and right (right) hemispheres. Colored areas indicate clusters exhibiting between-group differences in cortical volume for the control group versus the ADHD+ODD group comparison. Results are uncorrected for multiple comparisons, $p < .0001$. Yellow indicates the center of gravity for the clusters. Dark gray = sulci; light gray = gyri. *Note.* The Figure is only to illustrate the findings and to give an indication of the distribution of the effects, and is based on a whole brain voxel-wise approach rather than the ROI approach that is described in the manuscript.

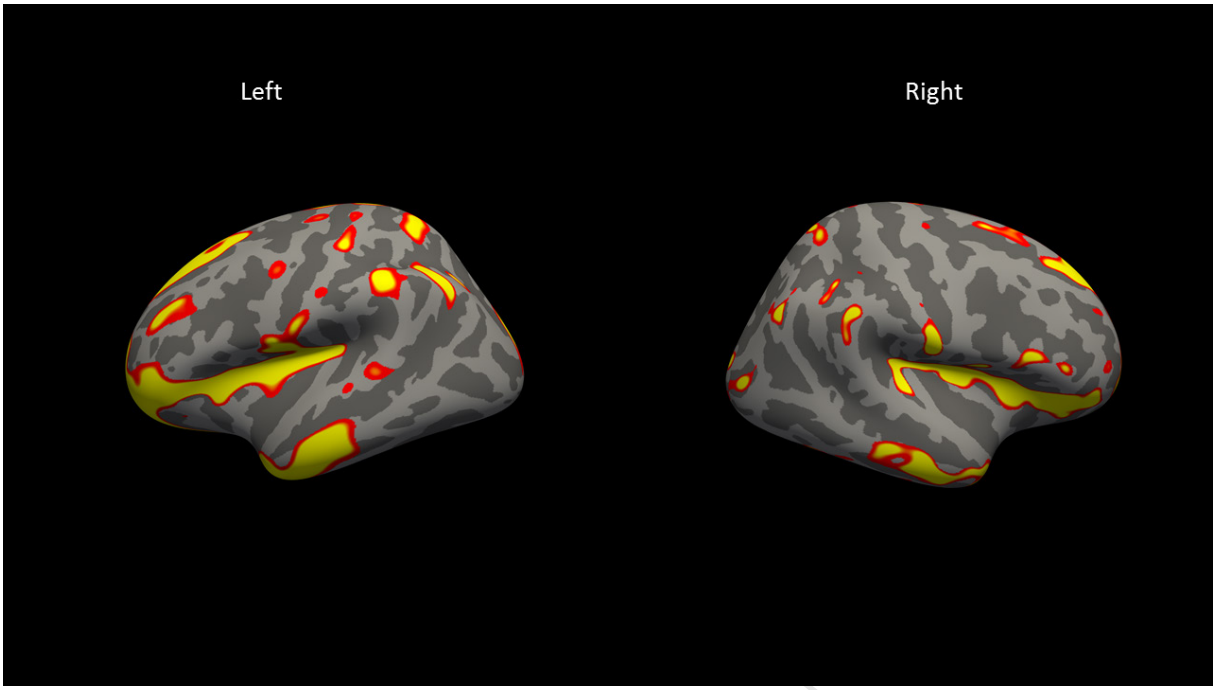


Figure S3. Volumetric group differences between the ADHD-only group and the ADHD+ODD group based on whole brain voxel-wise analyses.

Lateral view of the left (left) and right (right) hemispheres. Colored areas indicate clusters exhibiting between-group differences in cortical volume for the ADHD-only group versus the ADHD+ODD group comparison. Results are uncorrected for multiple comparisons, $p < .0001$. Yellow indicates the center of gravity for the clusters. Dark gray = sulci; light gray = gyri. *Note.* The Figure is only to illustrate the findings and to give an indication of the distribution of the effects, and is based on a whole brain voxel-wise approach rather than the ROI approach that is described in the manuscript.

Supplemental References

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